

Amendments to the Claim:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1 (currently amended). A process for production of recombinant ~~arylsulphatase~~ arylsulfatase A (ASA) in a continuous cell culture system, the process comprising:

- i) continuously culturing a mammalian cell capable of producing said arylsulfatase A in liquid medium ~~in a system comprising one or more bio-reactors; and~~
- ii) concentrating, purifying and formulating the recombinant rhASA by a purification process comprising one or more steps of affinity chromatography and/or ion exchange chromatography,

wherein the concentration and purification process of (ii) comprises a polishing step including a passive step, wherein the arylsulfatase A passes through a cation exchange chromatography resin or membrane and/or affinity chromatography resin, and an active step, wherein the arylsulfatase A is detained within and subsequently eluted from an anion exchange membrane or resin, and wherein the cation exchange chromatography resin or membrane and the anion chromatography exchange membrane or resin are coupled or connected in a series,

wherein said mammalian cell comprises a nucleotide sequence which encodes a polypeptide comprising (a) SEQ ID NOS:2 or 4 or (b) a mutant sequence at least 95% identical to SEQ ID NOS:2 or 4, and wherein said polypeptide, or a post-translationally modified product thereof that is produced by said cell, has arylsulfatase A activity.

2-7 (cancelled).

8 (previously presented). A process according to claim 1, wherein the mammalian cells are of human or primate origin.

9 (previously presented). A process according to claim 1, wherein the concentration and purification process of ii)

comprises one or more steps of Expanded Bed Chromatography.

10 (cancelled).

11 (currently amended). A process according to claim 1, wherein the concentration and purification process of ii) comprises the following steps:

- II) contacting an arylsulfatase A containing supernatant on an equilibrated chromatography column and eluting one or more fraction(s) containing arylsulfatase A;
- III) loading the fraction(s) from step II on another equilibrated chromatography column and eluting one or more fraction(s) containing arylsulfatase A;
- IV) buffer exchange of the arylsulfatase A present in the fraction(s) from step III by tangential flow filtration;
- V) polishing the preparation of arylsulfatase A from step IV in one or two or more successive steps, each step comprising loading the preparation on an equilibrated chromatography columns and eluting one or more fraction(s) containing arylsulfatase A;
- VI) passing the fraction(s) from step V through a viral reduction filter and/or inactivating virus in said fraction(s) with a virus inactivating agent;
- VII) formulating the fraction(s) from step VI in order to obtain a preparation of arylsulfatase A in a suitable formulation buffer;
- VIII) optionally filling the formulated preparation of arylsulfatase A into a suitable container and freeze-drying the sample.

12 (original). A process according to claim 11, further comprising an initial step I) of concentrating the arylsulfatase A by tangential flow filtration.

13 (previously presented). A process according to claim 11, wherein the chromatography column used in step II of the purification process is an anion exchange column.

14 (original). A process according to claim 13, wherein said anion exchange column is a DEAE Sepharose column or a DEAE Streamline column.

15 (previously presented). A process according to claim 11, wherein the chromatography column used in step III of the purification process is a hydrophobic interaction column.

16 (previously presented). A process according to claim 11, wherein purification of the sample in step IV of the purification process is accomplished by tangential flow filtration.

17 (cancelled).

18 (currently amended). A process according to claim 11, wherein the ~~filtration of the sample as performed in step VI of the purification process is replaced by or combined with contacting the sample with inactivating agent is a detergent, preferably prior to step V or preferably prior to step II of the purification process.~~

19-41 (cancelled).

42 (new). The process of claim 1 wherein the continuous culturing is for a period of at least one week.

43 (new). The process of claim 1 wherein the arylsulfatase has a specific arylsulfatase A activity of at least 20 units/mg.

44 (new). The process of claim 1 wherein the mutant sequence is at least 96% identical to SEQ ID NO:2 or 4.

45 (new). The process of claim 1 wherein the mutant sequence is at least 97% identical to SEQ ID NO:2 or 4.

46 (new). The process of claim 1 wherein the mutant sequence is at least 98% identical to SEQ ID NO:2 or 4.

47 (new). The process of claim 1 wherein the mutant sequence is at least 99% identical to SEQ ID NO:2 or 4.

48 (new). The process of claim 1 wherein the polypeptide comprises SEQ ID NOS:2 or 4.

49 (new). The process of claim 1 wherein the produced arylsulfatase A consists of SEQ ID NO:3.

50 (new). The process of claim 1 wherein the nucleotide

sequence encodes a polypeptide consisting of (a) SEQ ID NOS:2 or 4 or (b) a mutant sequence at least 95% identical to SEQ ID NOS:2 or 4, and wherein said polypeptide, or a post-translationally modified product thereof that is produced by said cell, has arylsulfatase A activity.

51 (new). The process of claim 1 wherein the encoded polypeptide, when aligned by sequence alignment software to SEQ ID NO:2 or 4, has a cysteine in the position aligned with Cys-69 in SEQ ID NO: 2 or Cys-51 in SEQ ID NO:4.

52 (new). The process of claim 51 wherein a linear sequence of five amino acids within said polypeptide, and including said cysteine, is identical to the aligned sequence of five amino acids in SEQ ID NO:2 or SEQ ID NO:4.

53 (new). The process of claim 51 wherein a linear sequence of nine amino acids within said polypeptide, and including said cysteine, is identical to the aligned sequence of nine amino acids in SEQ ID NO:2 or SEQ ID NO:4.

54 (new). The process of claim 51 wherein a linear sequence of twenty amino acids within said polypeptide, and including said cysteine, is at least 95% identical to the aligned sequence of twenty amino acids in SEQ ID NO:2 or SEQ ID NO:4.

55 (new). The process of claim 51 wherein a linear sequence of twenty amino acids within said polypeptide, and including said cysteine, is identical to the aligned sequence of twenty amino acids in SEQ ID NO:2 or SEQ ID NO:4.

56 (New). The process of claim 51 wherein the encoded polypeptide comprises at least one putative N-glycosylation site.

57 (New). The process of claim 51 wherein at least putative N-glycosylation site is phosphorylable.

58 (New). The process of claim 51 wherein the encoded polypeptide, when aligned by sequence alignment software to SEQ ID NO:2 or 4, has asparagine in the positions aligned with Asn-158 and Asn-350 in SEQ ID NO: 2 or Asn-140 and Asn-332 in SEQ ID NO:4 .

59 (New). The process of claim 58 wherein the encoded

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polypeptide, when aligned by sequence alignment software to SEQ ID NO:2 or 4, has asparagine in the position aligned with Asn-184 in SEQ ID NO: 2 or Asn-166 in SEQ ID NO:4.